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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,506	10/17/2001	Gregory R. Chiklis	19383-014	6911

26712 7590 01/28/2008
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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	

MAIL DATE	DELIVERY MODE
01/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/981,506	CHIKLIS ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-11,13-63,65,66 and 68-71* is/are pending in the application.

4a) Of the above claim(s) *2-11,16-48,53-59,62,63,65,66,68,69 and 71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,13-15,49-52,60,61 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 22 October 2007 has been entered.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

DETAILED ACTION

Claims 1, 12, 64 and 67 have been cancelled. Claims 2-11, 13-63, 65, 66, and 68-71 are pending. Claims 5-11, 16-48, 53-59, 62, 63, 65, 66, 68, 69 and 71 are drawn to a nonelected subject matter and hence are withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 2-4, 13-15, 49-52, 60, 61 and 70 are currently examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 2-4, 14, 15, 49-52, 60, 61, and 70 under 35 U.S.C. §103(a) as being unpatentable over Shepard *et al.* (April 2000) in view of Grovit-Ferbas *et al.* (July 2000, IDS filed on 24 April 2006) is **maintained** for the following reasons:

The instant invention is a composition comprising a purified nonpathogenic microorganism, especially an HIV, and liquid matrix comprising biological fluid; and a kit comprising the composition. The microorganism is rendered non-pathogenic by covalent attachment of a chemical compound on the surface proteins of the microorganism.

Shepard *et al.* disclose a composition comprising HIV-1 RNA in a liquid matrix such as blood, cerebral spinal fluid, saliva, breast milk, seminal plasma, and cervical-

vaginal lavage fluid. The HIV-1 RNA sample is subject to nucleic acid amplification (Abstract). Shepard *et al.* do not teach purifying and rendering non-pathogenic microorganisms by covalent attachment of a compound to surface proteins.

Grovit-Ferbas *et al.* describe chemical inactivation of HIV-1 (Abstract) in formaldehyde and virus purification by ultrafiltration (p.5803, Fractionation of virion-bound and soluble gp120 and Fractionation of virus on Percoll gradient). Formaldehyde (10% ultrapure; Polysciences) was freshly diluted in phosphatebuffered saline (PBS) and added to the virus as indicated. After incubation, an equal volume of 0.2% bovine serum albumin (BSA) in PBS was added to quench residual aldehyde. The buffer was removed by diafiltration in a 100-kDa-cutoff ultrafiltration device (Millipore) by centrifugation at 10,000 rpm. The purified and inactivated viruses are added with PBS (which is encompassed by the claim limitation "liquid matrix") to reconstitute the sample to the original volume. See page 5803, 1st column, 3rd full paragraph. This inactivation method renders a virus that is inactivated and still associates with envelope through *purification by ultrafiltration*. See the paragraph bridging pages 5802-5803. The samples are held at 4°C before ananalysis by ELISA. See page 5803, 1st column, second to the last paragraph. See also Figure 2, page 5804.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the virus sample of Shepard *et al.* by inactivating the virus-containing biological sample with the chemical treatment as taught by Grovit-Ferbas *et al.* The skilled artisan would have been motivated to do so to create a safe nonpathogenic positive control sample. There would have been a reasonable

expectation of success, given that the chemical treatment inactivates HIV-1 by at least 7 logs and still associates with envelope through purification by ultrafiltration, as taught by Grovit-Ferbas *et al.* Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants argue that the non-pathogenicity of the present method is achieved without the use of thermal treatments but Grovit-Ferbas *et al.* do not disclose rendering a virus non-pathogenic without the use of thermal treatment. Applicants' arguments have been fully considered but are not persuasive. Grovit-Ferbas *et al.* specifically disclose rendering a virus non-pathogenic at different temperatures, *i.e.* 4°C, 37°C, 45°C, 56°C and 62°C, to show how thermal treatment of HIV-1 retains antigenic properties (Figure 1, page 5804), which is not germane to the present rejection. Since the instant claims do not limit the temperature at which the surface proteins are irreversibly modified by covalent attachment of a compound comprising one or more reactive functional groups to one or more reactive sites on the surface proteins, Applicants' arguments pertaining to thermal treatment are irrelevant to the present rejection. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (*i.e.,* without the use of thermal treatment) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants assert that the chemical treatment for inactivating a virus as taught by Grovit-Ferbas *et al.* would not result in a purified and non-pathogenic microorganism. The word "inactivated" as used by Grovit-Ferbas *et al.* is fully encompassed by the limitation "non-pathogenic" in the instant claim. Applicants further that adding formaldehyde to samples as taught by Grovit-Ferbas *et al.* would not result in a purified microorganism. This assertion mischaracterizes the teachings by Grovit-Ferbas *et al.* Grovit-Ferbas *et al.* clearly state virus purification by ultrafiltration at the bottom of page 5802, 2nd column. The details involving ultrafiltration followed by Percoll gradient ultracentrifugation are taught on page 5803 in the 1st column. This density gradient ultracentrifugation is well recognized in the art as a virus purification method. Absence evidence to the contrary, Gorvit-Ferbas *et al.* therefore discloses the claim non-pathogenic purified microorganism, wherein the surface proteins have been irreversibly modified by covalent attachment of a compound comprising one or more reactive functional groups to one or more reactive sites on said surface proteins.

Applicants also argue that *adding* the chemically modified virus of Grovit-Ferbas *et al.* to the samples described by Shepard *et al.* would not provide a "control" since the added virus would merely increase the molarity of RT-PCR primer binding sequences in the sample. However, the examiner never suggested adding more of the target virus to the sample for nucleic acid amplification. It appears that Applicants have misconstrued the outstanding rejection. The suggestion to apply the formaldehyde-inactivation technique of Grovit-Ferbas *et al.* to a virus sample before nucleic acid amplification as disclosed in Sherpard *et al.* is well within knowledge generally available to one of

ordinary skill in the art. The formaldehyde inactivation method is a general technology that can be applied to any pathogenic samples before analysis for increase safety in handling the samples. Absent evidence to the contrary, one would reasonably expect the virus-containing biological sample of Shepard *et al.* to be suitable for nucleic acid amplification after treatment with formaldehyde, purification, and reconstitution in a biological fluid like PBS as suggested by Grovit-Ferbas *et al.* The suggestion or motivation to modify the reference does not have to be in the references themselves. See MPEP §2142. In this case, the motivation to combine the teachings of the Grovit-Ferbas and the Sherpard reference is immediately apparent. Therefore, a *prima facie* case of obviousness is properly established.

The rejection of claims 2-4, 13-15, 49-52, 60, 61, and 70 under 35 U.S.C. §103(a) as being unpatentable over Shepard *et al.* (April 2000) in view of Grovit-Ferbas *et al.* (July 2000, IDS filed on 24 April 2006) and Norman *et al.* (1970) is **maintained** for the following reasons:

The instant invention is further limited to modifying the liquid matrix for lyophilization.

The relevance of Shepard *et al.* and Grovit-Ferbas *et al.* is set forth above. Neither reference teaches the preparation of the liquid matrix for lyophilization.

Norman *et al.* teach the preservation of microorganisms by adding to the suspending fluid of sucrose to a final concentration of 12% volume-by-volume (p.69, right column, line no. 8-14) for lyophilization (Title).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the virus sample of Shepard *et al.* by inactivating the virus-containing biological sample with the chemical treatment as taught by Grovit-Ferbas *et al.* and by adding sucrose as suggested by Norman *et al.* The skilled artisan would have been motivated to do so for the ease of handling and transporting lyophilized samples as well as long term storage and stability. There would have been a reasonable expectation of success, given that the sucrose-lyophilized samples enhance the recovery of freeze-dried microorganisms, as taught by Norman *et al.* Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicants argue that, since the presently claimed invention is patentable over the references of Shepard *et al.* and Grovit-Ferbas *et al.*, the additional teaching of adding sucrose to pathogenic mycoplasma in Norman *et al.* is inadequate to maintain the rejection. Since Applicants used the same arguments as above against the Shepard and Grovit-Ferbas references, the rejection is maintained for the reasons already indicated above.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
04 Januay 2008

Louise Humphrey, Ph.D.
Assistant Examiner